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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/525,449	11/09/2005	Isabelle Poquet	1169-034	3827

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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
10/07/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/525,449	POQUET ET AL.	
	Examiner	Art Unit	
	MARIA B. MARVICH	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-34* is/are pending in the application.

4a) Of the above claim(s) *22-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-21 and 31-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/24/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 12-34 are pending in this application.

Election/Restrictions

Applicant's election without traverse of Group I (claim 12-21 and newly added 31-34) in the reply filed on 7/14/08 is acknowledged. Claims 22-30 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 7/14/08.

Priority

In an amendment filed 2/24/05, applicants have amended the priority data to read that the instant application is based on International Application No. PCT/FR 2003/002606 filed August 29,2003, and claims priority from, France Application Number 02 10805. While the priority claim reads that the instant application is based on International Application No. PCT/FR 2003/002606, it is unclear from this statement if the instant application is a continuation or 371. According to the MPEP 1895.01, the specific reference must identify the parent international application by international application number and international filing date and indicate the relationship of the applications (i.e., continuation, continuation-in-part, or division). An example of an appropriate first sentence of the specification is, for example, "This is a continuation of International Application PCT/EP2004/000000, with an international filing date of January 5, 2004, now abandoned."

Specification

The disclosure is objected to because of the following informalities: the specification lacks a Brief Description of Drawings.

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
(f) BACKGROUND OF THE INVENTION.
    (1) Field of the Invention.
    (2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

.Appropriate correction is required

Claim Objections

Claims 12-16, 18-20 and 31-34 are objected to because of the following informalities: The recitation in claim 12 "hereafter called" is unnecessary if the claim is amended to recite --a bacterial promoter (p_{zn})--. As well, the phrase "represent" and "exhibiting" do not convey with precision the relationship between the sequences and function. The claims should be amended to recite --TTGACA is the -35 box-- and --a polypeptide with at least--. Similar amendment to claim 13 for recitation of "represents" is recommended.

In claim 14, the phrase "the sequence" is unnecessary as it is redundant with the recitation (SEQ ID NO:4) and can be deleted.

In claims 16 and 18, it is improper to refer to a previous limitation or claim using the article "An". Rather the claim should be amended to recite --The expression cassette of claim 12 further comprising--.

As well for clarity in claim 16 the relationship between the element will be clearer of recited --a nucleotide sequence encoding an extracellular targeting peptide operably linked to a restriction site for cloning a nucleotide sequence as a translational fusion with said retargeting peptide, wherein the targeting peptide and the restriction site are--. Similarly, in claim 18 the claim should be amended to delete "into an expression cassette as claimed in Claim 12" and --wherein the expression cassette does not comprises-- as opposed "with the exclusion of the expression cassettes comprising".

In claim 17, the claim recites "said extracellular targeting peptide is a signal peptide is sequence: MKKINLALLTLATLMGVSSTAWFA (SEQ ID NO:6)". A reading of the specification supports a reading of the claims that --said extracellular targeting peptide is MKKINLALLTLATLMGVSSTAWFA (SEQ ID NO:6)--. The previous recitation suggests that the extracellular targeting peptide is a signal peptide found within SEQ ID NO:6.

The article "an" in claim 19 should be amended to --the-- as the expression cassette in claim 12 is a previously recited limitation.

Similarly, in claim 20 the recitation "at least one" should be amended to --the-- for proper antecedent basis.

Claims 31-34 recite "wherein sequence b) encodes polypeptide exhibiting". For clearer antecedent basis, this phrase should be amended to --wherein the sequence encoding the polypeptide has--.

Appropriate correction is required.

Claim 15 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The limitations recited in claim 15 are already recited in claim 12. As it is not clear if these are duplicate elements in the cassette or not.

Claim Rejections - 35 USC § 112, first paragraph

Claims 12-21 and 31-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an expression cassette comprising SEQ ID NO:1 operably linked to nucleotides 357-794 of SEQ ID NO:2 further operably linked to a restriction site, does not reasonably provide enablement for any other embodiment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples~ state of the art, predictability of the art, the amount of experimentation necessary and the relative skill levels of those in the art. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

The instant claims are drawn to a cassette designed for zinc-regulated expression of genes in gram-positive bacteria. The invention is based upon the observation that the ZitR repressor can bind and form a complex with affinity for the -35 box of SEQ ID NO:1 to repress transcription. In the absence of zinc, transcription ensues. Hence, applicants propose use of promoter elements comprising SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:4 and SEQ ID NO:5 which share the common feature of the -35 box of the *Lactococcus lactis* operon promoter which also serves as the binding site for ZitR.

The constructs of the instant invention also include 1) insertion sites for nucleotides of interest to be expressed under control of pzn 2) excludes inclusion of ZitS and a reporter gene 3) inclusion if a signal peptide to create fusion peptides comprising the signal peptide.

Case law has established that ' (t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.'" In re Wright 990 F.2d 1557, 1561. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that ' (t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". In this case, applicants disclose that the coding sequence of ZitR is found in figure 2 and hence applicants only disclose a single example of *Lactococcus lactis* ZitR. However, the claims are directed at a large and potentially diverse number of sequences by recitation of sequences with 80% to 95% identity for which it would require undue experimentation to identify those peptides that can function in the recited invention. First, the specification teaches that there is only one Lactococcus lactis ZitR sequences and presents this sequence in figure 2. The lack of guidance as to the structural requirements of this sequence exacerbates the ability to identify like sequences that can provide the same function. While recombinant technology for the generation of fragments is highly developed, the ability to determine *a priori* whether a fragment or related sequence can function in the recited invention is not.

A review of this art demonstrates that the ability to *de novo* protein model is not routine but requires vast computation even a single mutation can greatly effect even simple structural formations of the resultant protein.. A particular protein sequence determines the protein's structural, and functional properties, and a predictability of a representative number of claimed polypeptide sequences that display noteworthy biological properties requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of

modification and which are conserved (i.e., expectedly intolerant to modification), and detailed knowledge of the ways in which a protein's structure relates to its functional usefulness(see Guo et al and Lesk et al). Hence, the ability to determine a priori whether a homologue or variant can function in the recited invention is not a high art. A particular protein sequence determines the protein's structural, and functional properties, and a predictability of a representative number of claimed polypeptide sequences that display noteworthy biological properties requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e., expectedly intolerant to modification), and detailed knowledge of the ways in which a protein's structure relates to its functional usefulness. One of skill in the art would recognize that analyzing all permutation s of sequences comprising any combination of minimally 38 mutations to maximally 100 nucleotides would require undue experimentation despite the demonstration of protocols to do so.

In view of the unpredictability of the art of predicting the functional and structural nature of related sequences of SEQ ID NO 1, 3 or 5 or that encode SEQ ID NO:2, 4 or 6: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Given the unpredictability of the art, the poorly developed state of the art with regard to predicting the structural/ functional characteristics of a protein from primary sequence alone, the lack of adequate working examples and the lack of guidance provided by applicants, the skilled artisan would have to have conducted undue, unpredictable experimentation to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 12-15, 19-21 and 31-34 are rejected under 35 U.S.C. 102(b) as being anticipated by Poquet et al (J Bacteriology, 1998, Vol 180, pages 1904-1912; see entire document).

The vector of Poquet is also provided in U95834 in the plasmid pFUN. This plasmid comprises genomic DNA from *Lactococcus lactis* comprising the promoter of SEQ ID NO:5 for example. The instant specification teaches that the "promoter-regulator system of the MG1363 strain is obtained by PCR amplification (DyNAzyme EXT kit from Finnzymes) of part of the $P_{ZnzitRzitS'}$ insert (GenBank U95834) of the plasmid pVE8020, with the oligonucleotides oligo 9 and oligo MUT." As demonstrated in figure 2, this encompasses ZitR sequences. Hence, the vector and cassette of Poquet et al comprises the promoter and ZitR sequences. Insertion of the genomic sequences into the BamHI site does not appear to abolish the BamHI site, absent evidence to the contrary, into which additional sequences can be cloned. It is noted that Poquet also teaches identification of a signal sequence of SEQ ID NO:6 (Exp4, table 1).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARIA B. MARVICH whose telephone number is (571)272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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